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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/498,098	02/04/2000	Jeffrey Stack	AURO1330	8316

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/498,098	STACK, J. ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-38,40,50,60 and 80-87* is/are pending in the application.

4a) Of the above claim(s) *55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-38,40,50,60 and 80-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/14/05 has been entered.

The amendment filed 2/14/05 is acknowledged. The amendment has been entered. Claims 1-9, 11-38, 40, 50, 55, 60 and 80-87 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

Claim 55 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/2/2001.

Claims 1-9, 11-38, 40, 50, 60 and 80-87 are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

It is noted that upon further consideration it was determined that the instant claims encompass not only transgenic organisms and methods of using the transgenic organisms, but also in vivo methods including therapeutic methods (e.g., gene therapy). Therefore, the instant rejection is set forth in view of the new consideration for the reasons indicated below.

Claims 1-9, 11-15, 18-28, 30-38, 40, 60 and 83-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods wherein the methods are performed in cells that are *in vitro* as well as the claimed host cell wherein the host cell is *in vitro*, does not reasonably provide enablement the claimed methods wherein methods are performed in cells that are *in vivo* or for a non-isolated host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses how a cell can be engineered to express the chimeric destabilized polypeptide in vitro by transducing a nucleic acid encoding the chimeric polypeptide into a cell in vitro (see Example 8, page 74 of the specification). Furthermore, the specification contemplates transgenic animals comprising a nucleic acid sequence encoding the chimeric polypeptide and methods of making and using the transgenic animals (see p. 8 of the specification; as well as pages 59-62). Therefore, the claims clearly encompass methods

transgenic organisms. Furthermore, given the broadest reasonable interpretation, a "host cell" encompasses a cell in a transgenic organism.

The specification also indicates that the invention can be used for testing therapeutic molecules (e.g., see page 49, line last paragraph) and also contemplates pharmaceutical compositions comprising the therapeutic molecules as well as treatment methods (e.g., see page 53-59). Therefore, given the broadest reasonable interpretation, the claims also encompass therapeutic methods since the claims embrace regulating the concentration of a target protein (e.g., a therapeutic protein) in a cell *in vivo*.

As such, the claims are very broad and embrace transgenic organisms (including animals, plants and insects) engineered to express the chimeric destabilized polypeptide (including host cells within the transgenic organism) as well as therapeutic methods.

There is no evidence presented in the specification that any transgenic multicellular organisms that express the chimeric polypeptide have been successfully produced. Furthermore, the specification does not disclose that the methods have effectively treated any disease or disorder.

First, with respect to the claims as they encompass transgenic organisms, the state of the art at the time of filing regarding the production of transgenic organisms was and continues to be unpredictable. For instance, it is well known in the art that the level and the specificity of expression of a transgene, as well as the phenotype are greatly dependent on the specific transgene construct used. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the site of integration, etc. are all important factors in controlling the expression of the transgene. The art also recognizes problems with

regard to producing animals of different species with identical phenotypes even when using a particular transgene to create both transgenic animals. For example, Wall (Theriogenology, Vol. 45, pages 57-68, 1996; previously cited) teaches the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Furthermore, Overbeek (Transgenic Animal Technology, pages 96-98, 1994; previously cited) teaches that there can be considerable variation in the level of transgene expression in different transgenic animals (page 96, last paragraph). Therefore, the prior art recognized that creating transgenic organisms having a particular desired phenotype is unpredictable. In the instant case, the particular desired phenotype is the expression of the chimeric polypeptide at level sufficient to perform the claimed methods.

In addition, the species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al. (1990; previously cited) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al. (1990 previously cited) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop similar phenotypes in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats (see Mullins et al., 1989; and Taurog et al., 1988,

both previously cited). Therefore, one of skill in the art cannot readily predict that any transgenic organism will have the desired phenotype of interest without actually creating the transgenic organism.

The claims encompass methods of using transgenic organisms expressing the chimeric polypeptide as well as method of using cells of said transgenic organisms. For instance, the claims encompass a method of detecting an activity in a cell *in vivo*; a method of regulating the concentration of a target protein in a cell *in vivo*; and a host cell expressing the chimeric protein wherein said cells can be cells in a transgenic organism.

The specification only discloses general methods for producing transgenic animals and transgenic plants (see pages 59-67). The specification does not disclose working examples or provide guidance which would overcome the art-recognized problems indicated above. Therefore, one of skill in the art could not predictably and reliably make the transgenic plants, animals or insects encompassed the claims without performing an undue amount of additional experimentation.

With respect to the claims as the read on therapeutic methods, the claims encompass administering a nucleic acid sequence encoding a chimeric polypeptide wherein the chimeric polypeptide comprises a destabilization domain, a target protein (i.e., a therapeutic protein), and a linker domain that links the destabilization domain and the target protein. When the chimeric molecule is expressed in a cell as a single molecule comprising the destabilization domain, the linker and the therapeutic protein, the chimeric molecule is rapidly degraded resulting in a relatively low concentration of the chimeric molecule. However, upon dissociation of the destabilization domain from the therapeutic protein, such as by cleavage of the linker, the

therapeutic protein is no longer destabilized and the concentration of the therapeutic protein in the cell increases, presumably resulting in a therapeutic effect. Therefore, the therapeutic method requires the delivery of the nucleic acid sequence(s) encoding the chimeric polypeptide to the specifically desired target cell, proper expression of the chimeric molecule in the target cell and further requires a second level of regulation via endogenous or exogenous factors that regulate dissociation the destabilization domain from the chimeric molecule. It is noted that the claims are not directed to the treatment of any particular disease; therefore, given the broadest reasonable interpretation, the claims encompass treating any disease or disorder.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable. For instance, **Anderson** (Nature 1998; 392(suppl):25-30) teaches,

> "The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease. (See p. 30, first paragraph)."

Dang et al. (Clin. Cancer Res. 5:471-474, 1999) teaches "Although significant progress has been achieved in our understanding of the limitations of gene therapy by suboptimal vectors, host immunological responses to the vectors, and the lack of long term stable expression, the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues" (page 474, col. 2, last paragraph).

With respect to using the claimed method for treating a disease, it is noted that the claims encompass treating any disease. Therefore, given the broadest reasonable interpretation, the claimed method can be interpreted as treating any disease, such as diabetes, by administering a polynucleotide encoding a therapeutic gene (such as insulin or an anti-apoptotic gene) to a subject in order to treat diabetes.

However, regarding gene therapy for diabetes, Levine (Mol. Med. Today 5:165-171; 1999) indicates many of the obstacles that need to be overcome in order to create an effective gene therapy for diabetes including gene transfer problems, cell transfer problems, and the responsiveness of the transduced cells to blood glucose levels. Levine focuses on gene transfer into pancreatic beta cells.

Regarding gene transfer into beta cells, Levine indicates that there are two general means by which therapeutic genes can be introduced into beta cells: by transducing the islet cells ex vivo and reintroducing the cells into the pancrease of the subject (see p. 165, last paragraph), and transfer of the therapeutic gene(s) into pancreatic beta-cells in vivo. However, Levine also indicates, "Successful islet cell transplantation has proved to be an elusive goal... (and) to date, there are no studies demonstrating that [in vivo gene transfer into beta-cells] can be done." (See p. 166).

Levine teaches that both type I and type II diabetes results in the apoptotic death of beta-cells (see p. 166-167) and further indicates that preventing beta-cell apoptosis may be potentially applicable to both type I and type II diabetes either by inhibiting apoptosis of beta cells before they die via gene transfer of anti-apoptotic genes such as Bcl-2 into the beta cells (e.g., see p. 168-169). However, gene transfer into beta cells is unpredictable as indicated above.

Furthermore, Levine also indicates that successful gene transfer into beta cells (either in vivo or ex vivo) and/or successful cell transplant are not the only obstacles to obstacle to overcome in order to effectively treat diabetes. Once the therapeutic gene(s) or cells are successfully delivered, the cells must be able to respond changes in blood glucose levels:

> "A definitive treatment for diabetes mellitus will be one that maintains a normal blood glucose concentration in the face of fluctuating dietary intake. To accomplish this there must be mechanisms to sense the amount of blood glucose coupled to rapid release of the right amount of insulin." (See p. 165, abstract).

Levine summarizes the state of gene therapy for diabetes by stating, "the ultimate goal of a definitive, permanent treatment of diabetes through gene therapy lies in the distant future." (p. 170, last paragraph).

In view of the teachings of Anderson, Deng and Levine, it is clear that gene therapy methods are unpredictable in nature. Furthermore, the specification does not disclose working examples or provide guidance which would overcome the art-recognized problems. Therefore, additional experimentation would be required in order to practice the invention to the full scope encompassed by the claims.

Therefore, in view of the breadth of the claims, the limited amount of direction and/or guidance provided in the specification, the art recognized unpredictability with respect to making the transgenic organisms encompassed by the claims as well as the art recognized unpredictability of gene therapy, and the limited working examples, it is concluded that an undue amount of experimentation is required for one skilled in the art to make and use the claimed invention to the full scope encompassed by the claims.

It is noted that limiting the claims to methods that are performed *in vitro* as well as limiting the "host cell" to an isolated host cell would obviate this rejection

Claims 1-9, 11-38, 40, 50, 60 and 80-87 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass a destabilization domain that is non-cleavable by I-NH-ubiquitin protein endoproteases. It is clear from the specification, as well as claims 6, 31 and 38 that the destabilization domain encompasses ubiquitin homologs that are at least 85% identical to the amino acid sequence of wild-type ubiquitin. Claim 11 also encompasses "a naturally fluorescent protein or homolog thereof".

Claims 1-9, 11-22, 80, 83 and 85-87 are drawn to a method of detecting a protease activity in a cell, wherein the method uses a molecule comprising a destabilization domain wherein the destabilization domain can be **a ubiquitin homolog that is at least 85% identical to the amino acid sequence of wild-type ubiquitin** (see claims 6-8). Additionally, the instant method encompasses a molecule comprising a reporter moiety wherein the reporter moiety can be **a naturally fluorescent protein or homolog thereof** (see claim 11).

Claims 23-37 and 81 are drawn to a method of regulating the concentration of one or more target proteins in a cell, wherein the method uses a molecule comprising a destabilization

domain wherein the destabilization domain can be **a ubiquitin homolog that is at least 85% identical to the amino acid sequence of wild-type ubiquitin** (see claim 31).

Claims 38, 40, 82 and 84 are drawn to a method of destabilizing a target protein in a cell comprising administering to said cell a nucleic acid encoding a molecule comprising destabilization domain, wherein the destabilization domain can be **a ubiquitin homolog that is at least 85% identical to the amino acid sequence of wild-type ubiquitin** (see claim 38).

Claims 50 and 60 encompass a nucleic acid encoding a molecule comprising destabilization domain, wherein the destabilization domain can be **a ubiquitin homolog that is at least 85% identical to the amino acid sequence of wild-type ubiquitin.**

It is noted that the specification defines homolog in the following manner,

"The term 'homolog' refers to two sequences or parts thereof, that are greater than, or equal to 85% identical when optimally aligned using the ALIGN program. Homology or sequence identity refers to the following. Two amino acid sequences are homologous if there is a partial or complete identity between their sequences. For example, 85% homology means that 85% of the amino acids are identical when the two sequences are aligned for maximum matching. Gaps (in either of the two sequences being matched) are allowed in maximizing matching; gap lengths of 5 or less are preferred with 2 or less being more preferred. Alternatively and preferably, two protein sequences (or polypeptide sequences derived from them of at least 30 amino acids in length) are homologous, as this term is used herein, if they have an alignment score of more than 5 (in standard deviation units) using the program ALIGN with the mutation data matrix and a gap penalty of 6 or greater." (See pages 13-14 of the specification).

Therefore, the claims encompass destabilization domains that are ubiquitin homologs at least 85% identical to the amino acid sequence of wild-type ubiquitin. Claim 11 also specifically encompasses homologs of a naturally fluorescent protein. There is insufficient written description provided in the specification for the homologs encompassed by the claims.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient

description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164).

In the instant case the claims encompass molecules including ubiquitin homologs and naturally fluorescent protein homologs which can be as much as 15% different at the sequence level. However, the specification does not indicate which 15% of sequence can be varied without changing the desired function of the molecule. In order to meet the written description requirement in the instant case, the specification would have to indicate the relationship between the structure of the molecule and function of the molecule such that one of skill in the art could determine, without performing additional experimentation, which homologs have the desired function and which homologs do not have the desired function. Here, the specification does not teach any structure-function relationship for the claimed homologs. Specifically, the specification does not teach the relevant structural/physical/chemical characteristics, such as the presence of certain functional domains or sequence motifs, which are critical to the function of the homologs. Therefore, the specification has not provided adequate written description for the homologs encompassed by the claims.

Specifically regarding the ubiquitin homologs encompassed by the claims, the specification has described a homolog of ubiquitin that has the desired function (retaining ubiquitin function while being non-cleavable by alpha-NH-ubiquitin-endoproteases). The specific ubiquitin homolog described by the specification is Ubiquitin G76V (a Gly to Val

substitution at amino acid 76 of ubiquitin). Therefore, with respect to the rejection of claims drawn to ubiquitin homologs, amending the claim to limit the destabilization domain to Ubiquitin G76V would obviate this rejection as it pertains to ubiquitin homologs.

Regarding the naturally fluorescent protein homologs, the specification does not teach any naturally fluorescent protein homologs. Amending the claims such that the claims were not drawn to the homologs would obviate this rejection. For instance, changing a naturally fluorescent protein homolog, to naturally fluorescent protein, would obviate the instant rejection as it pertains to naturally fluorescent protein homologs.

Response to Arguments

Applicant's arguments filed 2/14/2005 have been fully considered and are addressed below as they pertain to the pending rejections indicated above.

With respect to the written description rejection Applicants point out that the limitation "non-cleavable by alpha-NH-ubiquitin endoproteases" in the independent claims limits the dependent claim to ubiquitin homologs that are non-cleavable by alpha-NH-ubiquitin endoproteases. Applicants also assert that the specification for a particular mutation that prevents cleavage by the ubiquitin endoproteases (page 13, lines 9-19 of the specification). Applicants argue that the law does not require the Applicants to structurally identify each and every ubiquitin homolog.

In response, it is respectfully pointed out that although the specification contemplates mutations that prevent, or significantly reduce, the cleavage of ubiquitin multimers by ubiquitin protein endoproteases, the specification (page 13, lines 9-19) only specifically discloses mutation of a single amino acid: the glycine at amino acid residue 76. Furthermore, it is acknowledged that Applicants are not required to structurally identify each and every ubiquitin homolog encompassed by the claims. However, the specification must provide a description sufficient to indicate to one of skill in the art which homologs encompassed by the claims would have the required function, and which ones would not have the required function. In the instant case, Applicants claim a genus of ubiquitin homologs that are at least 85% identical to the amino acid sequence of wild-type ubiquitin and which are non-cleavable by the indicated ubiquitin protein endoproteases. The specification only describes homologs that are different at one specific amino acid position: glycine 76. The specification does not disclose which, if any, other amino acids can be altered and result in a homolog that is non-cleavable by the ubiquitin protein endoprotease. Therefore, further experimentation would be required in order to determine which other homologs that are at least 85% identical to wild-type ubiquitin are non-cleavable by the ubiquitin protein endoproteases. Since further experimentation is required, the specification has not adequately described the claimed genus of molecules.

Therefore Applicants arguments are not persuasive.

It also is respectfully pointed out that claim 11 encompasses homologs of naturally fluorescent protein, but the specification does not appear to describe any such homologs.

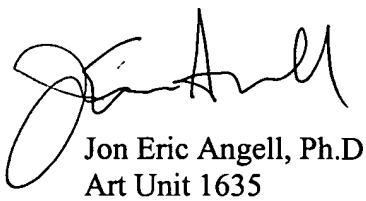
Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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